REMARKS

The Official Action of November 8, 1999 has been carefully considered and reconsideration of the application as amended is respectfully requested.

Claims 1 - 10 have been cancelled and rewritten as new claims 11 - 20. The recitations in new claims 11 - 14 correspond to the recitations in original claims 1 - 4. The recitations in new claims 16 - 20 correspond to the recitations in original claims 5 - 9. The recitations in new claim 15 draw support from the Examples in the specification which show the effectiveness of the claimed compound for use in monkeys and dogs (both mammals) and in the specification at, for example, page 11, which describes the administration of the claimed compound to a human (also a mammal).

The claims as rewritten are believed to be free of the rejections under 35 USC 112, second paragraph, raised in paragraphs 2a - f of the Official Action. In particular, the claims as rewritten do not contain a broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation. Moreover, the compound of formula (1) has been defined in each of the claims and the amount of the compound and the host also have been defined in all of the claims. Furthermore, the term "derivative" has been replaced with "compound" throughout the claims in accordance with the suggestion courteously made by the Examiner at paragraph 2(f) of the Official Action.

With respect to the rejection based upon the use of the terms "low", "high", and "lesser", Applicants respectfully submit that the claims as rewritten recite these terms in a manner that

would reasonably apprise those of skill in the art of the scope of the invention. In this respect, Applicants respectfully note that MPEP Section 2173.05(b) recognizes the acceptability of claim language including terms of degree even when a specification does not provide a standard for measuring that degree. The test is whether those of skill in the art would nevertheless be reasonably apprised of the scope of the invention. In the present case, Applicants have used the terms "high" and "lesser" in comparisons that would be clear to those of skill in the art. With respect to the term "slow", those of skill in the art would appreciate from the specification as filed that the enaminone functionality at the terminal nitrogen of the recited compound provides for metabolites of the recited compound with intact side chains that are less toxic than metabolites of compounds such as primaquine. This is because the enamione at the terminal nitrogen of the recited compound slows down chain degradation. (Oxidative metabolites of both N-alkylated and N-dealkylated origin produce secondary metabolites of o- or p- quinonoide nature after one electron oxidation.) Those of skill in the art would understand the scope of the applicable claim in this context.

It is believed that the claims as rewritten are free of the rejections noted at paragraphs 2a - f of the Official Action. Moreover, the claims as rewritten are believed to be sufficiently definite to satisfy the dictates of 35 USC 112, second paragraph.

With respect to the objection raised at paragraph 3 of the Official Action, the rejection has been rendered moot by cancellation of the applicable claim (original claim 10).

The claims have been rejected under 35 USC 102(b) as allegedly being anticipated by or, in the alternative, under 35 USC 103(a) as allegedly being obvious over Andersag. Applicants

respectfully traverse these rejections.

The Examiner contends that Andersag teaches the claimed compound at page 2, Example 11. However, Example 11 would appear to describe the condensation of several different compounds, none of which results in the claimed compound. The closest compound described in Example 11 would appear to be the one described at page 2, second column, lines 45 - 48. However, this compound differs from the claimed compound in a number of significant respects. First, the cited compound has a pentane portion with the amino group in the 8 position of the amino functionality bound to a $CH(CH_3)$ group. By contrast, the reference compound would have the amino group in the 8 position of its amino functionality bound to a CH_2 group rather than to a $CH(CH_3)$ group. This would clearly affect the properties of this amino position. Moreover, the reference compound would have a lactone group with a beta methyl substituent that is lacking from the claimed compound. Accordingly, it is respectfully believed to be incorrect for the Examiner to contend that the cited reference shows the claimed compound or anticipates the recited method.

With respect to the question of alleged obviousness, Applicants respectfully submit that the closest reference compound is not sufficiently structurally similar to the claimed compound to set forth even a *prima facie* case of obviousness for the recited compound. See, e.g., *In re Grabiak*, 226 USPQ 870 (Fed. Cir 1985); *In re Jones*, 21 USPQ 2d 1941 (Fed. Cir. 1992). In any event, the Examiner has the burden to explain any contention that the prior art compounds are sufficiently structurally similar to those claimed to give rise to a *prima facie* case (see *Ex parte Krepelka*, 231 USPQ 746 (BPAI 1986)). It is respectfully submitted that the Examiner has not and cannot satisfy this burden in the present case.

Moreover, the generic formula of the Andersag patent encompasses a vast number of compounds and there is nothing in the cited reference to show or suggest the selection from among those of the claimed compound (see *In re Baird*, 29 USPQ 2d 1550 (Fed. Cir. 1994)). *A fortiori* there is nothing in the cited reference to show or suggest the claimed method. In this respect, Applicants respectfully note that the cited reference contains a single general statement that the new products according to the Andersag invention are therapeutically useful as anaesthetics and parasiticides. Andersag does not discuss or even recognize differences between the biological activity or toxicity of any of the compounds described therein. When considered as a whole, the reference would not motivate one of skill in the art to make the recited compound with even a reasonable expectation that it would be therapeutically effective in treating malaria with low toxicity. The salient points are as follows:

i) Andersag relates to condensation products of acetylbutyrolactones and primary amines of the aromatic and heteroaromatic series. The patent does not disclose any biological activity of the amines used or their toxicity. The only disclosure relates to the reaction with therapeutically useful amines.

ii) Primaquine, of which the compound of formula (1) of the invention is a derivative with an enamionone functionality, itself and its toxic metabolites were developed much subsequent to the Andersag Patent. The specification of the present application provides a detailed description of prior art which includes disclosure of primaquine and its toxic metabolites.

iii) Insofar as the Examiner's observations regarding the inherency of the

gametocytocidal activity, low toxicity, controlled delivery facilitation, etc. are concerned, neither Andersag nor the aforementioned prior art described in the specification would provide even a reasonable expectation that putting enaminone at the terminal nitrogen atom would result in the slowing down of chain degradation, reduce methaemoglobin formation thereby lessening toxicity, or provide lower toxicity in terms of increased levels of glutathione. As is clear from the prior art, the high toxicity of primaquine affected its use as an antimalarial agent despite its otherwise demonstrable activity in terms of blood schizontocidal, tissue schizontocidal and gametocytocidal activity. The prior art metabolites of primaquine were either non-functional, or also responsible for its toxicity. The same would have been expected of the Andersag compounds.

iv) There is no teaching in the prior art that putting enaminone at the terminal nitrogen atom would lower the levels of oxidation of glutathione and reduce the levels of methaemoglobin formation thereby lessening toxicity.

v) Also, as is demonstrated in the specification on page 16, last paragraph, the use of primaquine *per se* causes drug induced haemolysis in persons deficient in G-6PD enzyme. The use of the compound of formula I of the invention, does not cause this result.

iv) The prior art does not show or suggest the enhanced or improved gametocytocidal activity of the compound of formula (I) of the invention. There is also no prior art disclosure or indication that the properties claimed in claim 1 or shown in the specification as being possessed by the compound of formula (I) are inherent chemical or/and physical properties of the Andersag compounds. On the contrary, the prior art suggests that primaquine and its metabolites actually are more toxic, and that some metabolites are also completely non-functional.

Under the circumstances, the method for using the compound of formula (I) as claimed in claims 11 - 19 cannot be said to be obvious from or anticipated by Andersag. The method of preparation should also therefore be considered to be nonobvious (see *In re Ochiai*, 37 USPQ 2d 1127 (Fed. Cir. 1995)).

In view of the above, it is respectfully submitted that the cited art cannot anticipate or render obvious the invention as now claimed. All rejections and objections of record are believed to have been successfully traversed and the application is believed to be in allowable form. An early Notice of Allowability is earnestly solicited and is believed to be fully warranted.

Respectfully submitted,

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